

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet associated intracranial haemorrhage
AUTHORS	John Batchelor

VERSION 1 - REVIEW

REVIEWER	Shan Yuan, MD Assistant Professor Division of Transfusion Medicine Department of Pathology and Laboratory Medicine David Geffen School of Medicine at UCLA Los Angeles, CA
REVIEW RETURNED	14/11/2011

THE STUDY	Minor editorial comment, in several places, including the title, the word "agents" should be inserted after "anti-platelet" for greater clarity.
GENERAL COMMENTS	This is a well-researched, well-written and balanced meta-analysis on the potential benefits of (or lack thereof) platelet transfusions in patients with spontaneous or traumatic intracranial hemorrhages while taking anti-platelet agents. As the administration of platelets has increasingly become routine practice in this setting despite the lack of evidence from a large, multicenter, randomized trial, a closer examination of available smaller, retrospective studies is warranted. The author concluded that platelet transfusion conferred no clear benefit in terms of reducing mortality in this setting. The author also did an excellent job summarizing and highlighting the limitations of this meta-analysis; only a handful of heterogeneous and relatively small studies met the inclusion criteria; the end points were variably defined; and that there might be an inherent bias in these non-randomized studies, as platelets were often transfused "at the discretion of the physician", hence it was likely that more patients with severe hemorrhages were included in the transfused than the control group. The authors showed that platelet transfusions may confer some benefit in patients with spontaneous bleeding –an interesting observation as one would indeed expect that underlying coagulopathies, including platelet dysfunctions, contributed more significantly to the development of intracranial bleeding in this group than in patients who had sustained head injuries. However, the author also pointed out that the difference did not reach statistical significance due to the small sample sizes, and furthermore reviewed other papers that failed to demonstrate an similar advantage. Yet another question that is unanswered by the available studies and this meta-analysis is whether the pharmacological properties of various anti-platelet agents (longer vs. shorter- acting, reversible vs. irreversible inhibitors) would impact how effective

	platelet transfusions can be in this setting. It is unclear from this manuscript, what proportions of patients included were taking the various anti-platelet agents, and it was also unclear whether it would have been possible to categorize the study patients by the antiplatelet agents they were taking, and how such analyses might have modified the conclusions of the study.
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REVIEWER	Maria I. Aguilar MD Associate Professor of Neurology Mayo Clinic Phoenix, AZ USA
REVIEW RETURNED	21/11/2011

The reviewer completed the checklist but made no further comments.

REVIEWER	Dr Simon Stanworth Consultant Haematologist NHS Blood and Transplant Level 2, John Radcliffe Hospital
REVIEW RETURNED	27/11/2011

THE STUDY	Please ensure PRISMA followed
GENERAL COMMENTS	<p>This paper describes a meta-analysis to determine the effects of platelet transfusions in intracranial haemorrhage. The topic is clinically important and clarity on treatment approaches in these patients on anti-platelet agents is required in clinical practice.</p> <p>In the background, the authors indicate variable practice, but that in some trauma centres platelet transfusions is standard. Can they provide more details - what is the evidence?</p> <p>The final sentence indicates that the aim was to determine by meta-analysis what the impact of platelet transfusions is. I would suggest that meta-analysis by itself cannot do this, but it can be a tool for hypothesis generation etc in new studies.</p> <p>How much of a limitation is searching by one database.</p> <p>Is Jadad really the most appropriate methodological tool for the types of included studies? My understanding it was set up for different type of interventional trials.</p> <p>The authors provide data on Q tests and I²; some justification for why both is needed. With the degree of heterogeneity noted, was quantitative analysis even appropriate?</p> <p>More information is required about the characteristics of the studies themselves and the patient populations, even down to details about the intervention eg dose of platelet transfusions etc. Much of this only comes out in the discussion, for each study in turn, and not in the results section. I would expect to see more qualitative reviewing of details across studies, rather than by individual study.</p> <p>The limitations of the studies themselves make any kind of conclusions very problematic, if at all.</p>

	<p>Do the discussion points about study outcomes etc inform the Dutch trial. Will this trial answer questions. What do the authors mean by the “relative importance of this subject”?</p> <p>Minor points: Is deduplication the right word, should platelet transfusions be a key word. The article summary says: Six studies were found to be “suitable” for the meta-analysis – were others not-suitable!?</p>
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VERSION 1 – AUTHOR RESPONSE

The following revisions have been made at the request of the review and editor.

1. The search strategy has been revised to include new terms.
2. Additional databases have also been searched.
3. A PRISMA flow diagram has also been included in the text.
4. All citations were reviewed by Alan Grayson. All papers which were selected by myself for the meta-analysis and were also reviewed by Alan Grayson. This should help to reduce any potential bias. Dr Grayson was also responsible for the major revision of the manuscript and has therefore been upgraded to co-author.
5. The comment regarding the Jadad Scoring of papers has been removed.
6. The comment made by one of the reviewers regarding why papers were not included has been re-emphasised in the PRISMA flow chart. Papers were not included if they did not meet the inclusion criteria. The majority of the full papers reviewed were in fact cohort studies examining the associated between aspirin and or anticoagulants and intracranial haemorrhage.
7. The I² test was included in this meta-analysis in view of the fact that some formal assessment of heterogeneity is an integral part of the meta-analysis. The Q test analysis was removed. Although the authors do accept the comment by one of the reviewers that testing for heterogeneity may have little statistical value in this particular meta-analysis due to the overt heterogeneity of the studies.
8. A substantial revision of both the results and the discussion has been performed so as to comply with the request of one reviewer. Namely study data has been transposed into the results section and removed from the discussion section.
9. It was not possible to perform a subgroup meta-analysis on the aspirin only group or the clopidogrel only group. This point has been reported and discussed in the text.
10. In the introduction the sentence “platelet transfusion has become standard practice” has been changed to “is practiced”. The evidence for this then becomes self evident from the text, based upon the review articles by Campbell and McMillan cited in the text and by the fact that all of the studies were retrospective cohort studies not randomised controlled trials.
11. The points in the discussion regarding the indication for a platelet transfusion for each study have been removed from the discussion section and placed in the results section. As requested by one of the reviewers.
12. Six studies were found to be “suitable” for the meta-analysis – were others not-suitable!? The PRISMA flow chart gives the number of papers rejected and the reasons why.
13. Deduplication does seem to be the correct word. The Editor may wish to clarify this point.
14. Will the Dutch trial answer the mortality trial answer question ?. The end point of the PATCH study may not determine the effect on mortality. The end points of this study have been provided in the text.
15. What does the “phrase the relative” importance mean ? The inference of this phrase is due to the large number of people now taking aspirin and the relative high frequency of ICH and head injuries does have potential resource implications with regard to platelet transfusion availability. This phrase has however been changed to “The current low level of evidence”

Yours Faithfully
Mr Batchelor and Alan Grayson